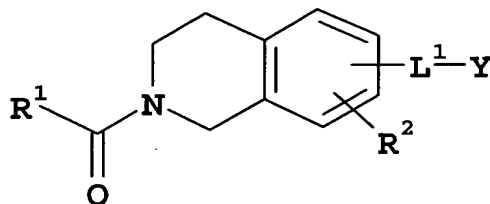


CLAIMS

What is claimed is:

- 5 1. A compound of formula (I):-



(I)

10 wherein:-

R¹ represents optionally substituted aryl, optionally substituted heteroaryl, R³NH-Ar¹-L²- or R³-NH-C(=O)-NH-Ar²-L²-;

R² represents hydrogen, halogen, C₁₋₄alkyl or C₁₋₄alkoxy;

R³ represents optionally substituted aryl or optionally substituted heteroaryl;

15 R⁴ is alkyl, aryl, cycloalkyl, heteroaryl or heterocycloalkyl, or alkyl substituted by aryl, an acidic functional group, cycloalkyl, heteroaryl, heterocycloalkyl, -S(O)_mR⁵, -C(=O)-NY³Y⁴ or -NY³Y⁴;

R⁵ represents alkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkylalkynyl, cycloalkenyl, cycloalkenylalkyl, heteroaryl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heterocycloalkyl or heterocycloalkylalkyl;

20 R⁶ is hydrogen, alkyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl or heterocycloalkylalkyl;

R⁷ is hydrogen, R⁵ or alkyl substituted with alkoxy, cycloalkyl, hydroxy, mercapto, alkylthio or -NY³Y⁴;

R⁸ is hydrogen or C₁₋₄alkyl;

25 R⁹ and R¹¹ are each independently selected from hydrogen or a group consisting of amino acid side chains, an acidic functional group, R⁵, -C(=O)-R⁵, or -C(=O)-NY³Y⁴, or alkyl substituted by an acidic functional group or by R⁵, -NY³Y⁴, -NH-C(=O)-R⁵, -C(=O)-R¹²-NH₂, -C(=O)-Ar²-NH₂, -C(=O)-R¹²-CO₂H, or -C(=O)-NY³Y⁴;

or R⁷ and R⁹ together with the atoms to which they attached form a 3- to 6-membered heterocycloalkyl ring;

R¹⁰ represents C₁₋₆alkylene, optionally substituted by R⁴;

R¹² is an alkylene chain, an alkenylene chain, or an alkynylene chain;

5 R¹³ is alkyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl or heterocycloalkylalkyl;

Ar¹ represents a saturated, partially saturated or fully unsaturated 8- to 10-membered bicyclic ring system containing at least one heteroatom selected from O, S or N, optionally substituted by one or more aryl group substituents;

10 Ar² represents aryldiyl or heteroaryldiyl;

L¹ represents

- (i) an alkenylene, alkylene or alkynylene linkage each optionally substituted by (a) carboxy, hydroxy, mercapto, cyano, oxo, -S(O)_mR⁴, R⁵, -C(=O)-R⁵, -C(=O)-OR⁵, -N(R⁶)-C(=O)-R⁴, -N(R⁶)-C(=O)-OR⁴, -N(R⁶)-SO₂-R⁴, -NY³Y⁴ or
 15 -[C(=O)-N(R⁷)-C(R⁸)(R⁹)]_p-C(=O)-NY³Y⁴; or by (b) alkyl substituted by carboxy, hydroxy, mercapto, imidazolyl, S(O)_mR⁴, -C(=O)-NY³Y⁴ or -NY³Y⁴;
- (ii) a -[C(=O)-N(R⁷)-C(R⁸)(R⁹)]_p- linkage;
- (iii) a -Z¹-R¹⁰- linkage;
- (iv) a -R¹⁰-Z¹-R¹⁰- linkage;
- 20 (v) a -C(R⁸)(R¹¹)-[C(=O)-N(R⁷)-C(R⁸)(R⁹)]_p- linkage; or
- (vi) a -L³-L⁴-L⁵- linkage;

L² represents an alkylene chain;

L³ and L⁵ each independently represent a direct bond or an alkylene chain;

L⁴ represents a cycloalkylene or heterocycloalkylene linkage;

25 Y¹ and Y² are independently hydrogen, alkenyl, alkyl, aryl, arylalkyl, cycloalkyl, heteroaryl or heteroarylalkyl; or the group -NY¹Y² may form a cyclic amine;

Y³ and Y⁴ are independently hydrogen, alkenyl, alkyl, alkynyl, aryl, cycloalkenyl, cycloalkyl, heteroaryl, heterocycloalkyl, or alkyl substituted by alkoxy, aryl, cyano, cycloalkyl, heteroaryl, heterocycloalkyl, hydroxy, oxo, -NY¹Y², or one or more -CO₂R⁶ or -C(=O)-NY¹Y² groups; or the
 30 group -NY³Y⁴ may form a 5- to 7-membered cyclic amine which (i) may be optionally substituted

with one or more substituents selected from the group consisting of alkoxy, carboxamido, carboxy, hydroxy, oxo (or a 5-, 6- or 7-membered cyclic acetal derivative thereof) and R^7 ; (ii) may also contain a further heteroatom selected from O, S, SO_2 , or NY^5 ; and (iii) may also be fused to additional aryl, heteroaryl, heterocycloalkyl or cycloalkyl rings to form a bicyclic or tricyclic ring system;

5 Y^5 is hydrogen, alkyl, aryl, arylalkyl, $-C(=O)-R^{13}$, $-C(=O)-OR^{13}$ or $-SO_2R^{13}$;

Z^1 is O, $S(O)_n$, NR^8 , SO_2NR^8 , $C(=O)NR^8$ or $C(=O)$;

Y is carboxy or an acid bioisostere;

m is an integer 1 or 2;

n is zero or an integer 1 or 2; and

10 p is zero or an integer 1 to 4;

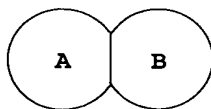
but excluding compounds where an oxygen, nitrogen or sulfur atom is attached directly to a carbon carbon multiple bond of an alkenylene or alkynylene residue;

and the corresponding N-oxides and ester prodrugs thereof, and the pharmaceutically acceptable salts and solvates of such compounds, and the N-oxides and ester prodrugs thereof.

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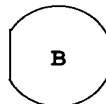
2. A compound according to claim 1 in which R^1 represents a group $R^3-NH-Ar^1-L^2$ - in which: L^2 is a straight or branched C_{1-6} alkylene chain;

Ar^1 is an 8- to 10-membered bicyclic system



in which (i) ring A is a 5- or

6-membered optionally substituted heterocycle, (ii) ring

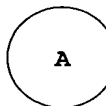


is a 5- or 6-membered optionally

20 substituted heterocycle or an optionally substituted benzene ring, and (iii) the two rings are joined together by a carbon-carbon linkage or a carbon-nitrogen linkage; and

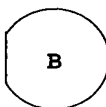
R^3 is an optionally substituted aryl.

3. A compound according to claim 2 in which



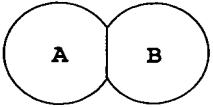
is a 5-membered optionally substituted

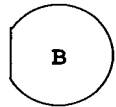
25 heterocycle, ring



is an optionally substituted benzene ring, and the two rings are joined

together by a carbon-carbon linkage.

4. A compound according to claim 2 in which  is an optionally substituted benzoxazolyl or an optionally substituted benzimidazolyl, each in which the benzene ring contains the optional substituents.

5. A compound according to claim 2 in which ring  is a benzene ring optionally substituted by one of C₁₋₄ alkyl, C₁₋₄ alkoxy, amino, halogen, hydroxy, C₁₋₄ alkylthio, C₁₋₄ alkylsulfinyl, C₁₋₄ alkylsulfonyl, nitro or trifluoromethyl.

6. A compound according to claim 2 in which R³ represents a 2-substituted phenyl.

10

7. A compound according to claim 6 in which R³ represents 2-methylphenyl.

8. A compound according to claim 1 in which R¹ represents a group R³-NH-C(=O)-NH-Ar²-L² in which:

15 L² is a straight or branched C₁₋₆alkylene chain;

Ar² is an optionally substituted phenylene or an optionally substituted heteroaryldiyl; and

R³ is an optionally substituted aryl group or an optionally substituted heteroaryl group.

9. A compound according to claim 8 in which Ar² is an optionally substituted m- or p-phenylene.

20

10. A compound according to claim 9 in which Ar² is a 3-substituted p-phenylene in which the substituent is ortho to the R³-NH-C(=O)-NH- group.

11. A compound according to claim 8 in which Ar² is an optionally substituted azaheteroaryldiyl.

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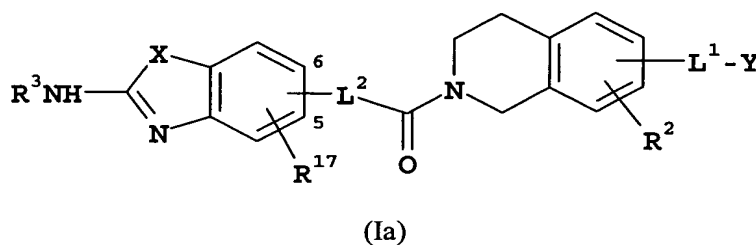
12. A compound according to claim 11 in which Ar² is pyridine-2,5-diyl, in which the R³-NH-C(=O)-NH- group is adjacent to the pyridyl nitrogen atom, and which is substituted in the 4- or 6-position with a methyl or methoxy group.

13. A compound according to claim 8 in which R³ is 2- or 3-methyl(or methoxy)phenyl.

14. A compound according to claim 8 in which R³ is an optionally substituted pyridyl.

5 15. A compound according to claim 14 in which R³ is 3-methyl-2-pyridyl.

16. A compound according to claim 1 of formula (Ia):-



10

in which R², R³, L¹, L² and Y are as defined in claim 1, X is O or NR¹⁸, where R¹⁸ is hydrogen or C₁₋₄alkyl, and R¹⁷ is hydrogen or an aryl group substituent, and the corresponding N-oxides and ester prodrugs thereof, and the pharmaceutically acceptable salts and solvates of such compounds, and the N-oxides and ester prodrugs thereof.

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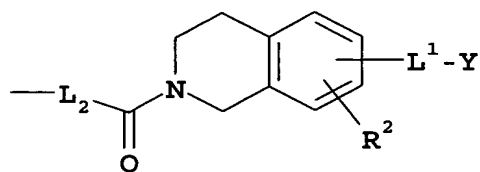
17. A compound according to claim 16 in which R³ represents an optionally substituted aryl.

18. A compound according to claim 16 in which R¹⁷ represents hydrogen, halo, C₁₋₄ alkyl, or C₁₋₄alkoxy.

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19. A compound according to claim 16 in which L² represents a straight or branched C₁₋₆alkylene chain.

25 20. A compound according to claim 16 in which the group

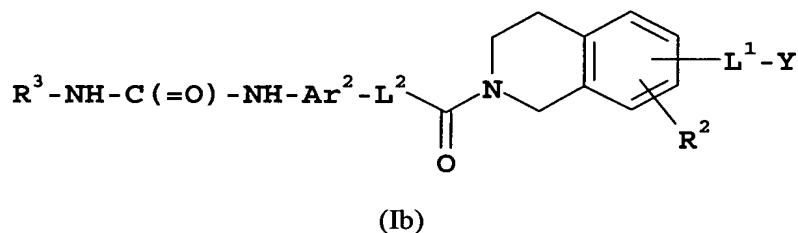


is attached at the ring 6 position or at the ring 5 or 6 position

when X is NR¹⁸ and R¹⁸ is C₁₋₄alkyl.

21. A compound according to claim 16 in which the group $\text{—L}^1\text{—Y}$ is attached at position 6 or 7 of the tetrahydroisoquinoline ring.

5 22. A compound according to claim 1 of formula (Ib):



10 in which R^2 , R^3 , Ar^2 , L^1 , L^2 and Y are as defined in claim 1, and the corresponding N-oxides and ester prodrugs thereof, and the pharmaceutically acceptable salts and solvates of such compounds, and the N-oxides and ester prodrugs thereof.

15 23. A compound according to claim 22 in which R^3 represents an optionally substituted aryl group or an optionally substituted heteroaryl group.

24. A compound according to claim 23 in which R^3 represents 2-methylphenyl or 3-methyl-2-pyridyl.

20 25. A compound according to claim 22 in which Ar^2 represents an optionally substituted phenylene or optionally substituted heteroaryldiyl.

26. A compound according to claim 25 in which Ar^2 is p-phenylene or p-phenylene substituted in the 3-position by halo, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkylthio, C_{1-4} alkylsulfinyl or C_{1-4} alkylsulfonyl.

25 27. A compound according to claim 25 in which Ar^2 is pyridine-2,5-diyl, in which the $R^3\text{—NH—C(=O)—NH—}$ group is adjacent to the pyridyl nitrogen atom, and which is substituted in the 4- or 6-position with a methyl or methoxy group.

30 28. A compound according to claim 22 in which L^2 represents a straight or branched C_{1-6} alkylene chain.

29. A compound according to claim 1 in which L^1 represents a C_{1-4} alkylene linkage optionally substituted by C_{1-4} alkyl, aryl, heteroaryl, $-N(R^6)-C(=O)-R^4$, $-N(R^6)-C(=O)-OR^4$, $-N(R^6)-SO_2-R^4$, $-NY^3Y^4$ or $-[C(=O)-N(R^7)-C(R^8)(R^9)]_p-C(=O)-NY^3Y^4$, or alkyl substituted by carboxy, hydroxy, mercapto, imidazolyl, $-C(=O)-NY^3Y^4$ or $-NY^3Y^4$.

30. A compound according to claim 29 in which the C_{1-4} alkylene linkage is an ethylene linkage.

31. A compound according to claim 30 in which L^1 represents a group $\begin{array}{c} R^{14} \\ | \\ -C-CH_2- \\ | \\ R^{15} \end{array}$, where

R^{14} is hydrogen or C_{1-4} alkyl and R^{15} represents hydrogen or C_{1-4} alkyl; or where R^{14} is hydrogen and R^{15} represents aryl, heteroaryl, $-N(R^6)-C(=O)-R^4$, $-N(R^6)-C(=O)-OR^4$, $-N(R^6)-SO_2-R^4$, $-NY^3Y^4$ or $-[C(=O)-N(R^7)-C(R^8)(R^9)]_p-C(=O)-NY^3Y^4$, or alkyl substituted by carboxy, hydroxy, mercapto, imidazolyl, $-C(=O)-NY^3Y^4$ or $-NY^3Y^4$.

32. A compound according to claim 30 in which L^1 represents a group $\begin{array}{c} R^{14} \\ | \\ -CH_2-C- \\ | \\ R^{16} \end{array}$, where

R^{14} is hydrogen or C_{1-4} alkyl and R^{16} represents C_{1-4} alkyl; or where R^{14} is hydrogen and R^{16} represents aryl, heteroaryl, $-N(R^6)-C(=O)-R^4$, $-N(R^6)-C(=O)-OR^4$, $-N(R^6)-SO_2-R^4$, $-NY^3Y^4$ or $-[C(=O)-N(R^7)-C(R^8)(R^9)]_p-C(=O)-NY^3Y^4$, or alkyl substituted by carboxy, hydroxy, mercapto, imidazolyl, $-C(=O)-NY^3Y^4$ or $-NY^3Y^4$.

33. A compound according to claim 32 in which L^1 is a group $\begin{array}{c} -CH_2-CH- \\ | \\ R^{16} \end{array}$, where R^{16}

represents $-N(R^6)-C(=O)-R^4$, or $-N(R^6)-SO_2-R^4$.

34. A compound according to claim 33 in which the group $\begin{array}{c} -CH_2-CH- \\ | \\ R^{16} \end{array}$ is $\begin{array}{c} -CH_2-CH- \\ | \quad \uparrow \\ R^{16} \quad R^{16} \end{array}$.

35. A compound according to claim 1 selected from:

3-(((4-methyl-2-*o*-tolylamino-benzoxazol-6-yl)-acetyl)-1,2,3,4-tetrahydro-isoquinolin-6-yl)-butanoic acid;

5 3-(((2-*o*-tolylamino-benzoxazol-6-yl)-acetyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl)-butanoic acid,;
3-phenyl-3-(((2-*o*-tolylamino-benzoxazol-6-yl)-acetyl)-1,2,3,4-tetrahydro-isoquinolin-6-yl)-propanoic acid;

3-cyclohexyl-3-(((2-*o*-tolylamino-benzoxazol-6-yl)-acetyl)-1,2,3,4-tetrahydro-isoquinolin-6-yl)-propanoic acid;

10 3-(pyrid-4-yl)-3-(((2-*o*-tolylamino-benzoxazol-6-yl)-acetyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl)-propanoic acid;

3-(((2-*o*-tolylamino-benzoxazol-6-yl)-acetyl)-1,2,3,4-tetrahydro-isoquinolin-8-yl)-but-2-enoic acid;

3-(((2-*o*-tolylamino-benzoxazol-6-yl)-acetyl)-1,2,3,4-tetrahydro-isoquinolin-8-yl)-butanoic acid;

3-{2-[(2-*o*-tolylamino-benzoxazol-6-yl)-carbonyl]-1,2,3,4-tetrahydro-isoquinolin-6-yl}-butanoic acid;

15 {5-(3-methoxy-4-[3-(2-methylphenyl)ureido]-phenylacetyl-amino)-1,2,3,4-tetrahydro-isoquinolin-8-yl}-butanoic acid;

2-(2,6-dichloro-benzoylamino)-3-[2-(2,6-dichloro-benzoyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl]-propionic acid;

3-phenyl-3-(((2-*o*-tolylamino-benzoxazol-6-yl)-acetyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl)-propanoic acid;

3-((2-*o*-tolylamino-benzoxazol-6-yl)-acetyl)-1,2,3,4-tetrahydro-isoquinolin-6-yl)-butanoic acid;

3-(pyrid-4-yl)-3-(((2-*o*-tolylamino-benzoxazol-6-yl)-acetyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl)-propanoic acid, enantiomer A;

3-(pyrid-4-yl)-3-(((2-*o*-tolylamino-benzoxazol-6-yl)-acetyl)-1,2,3,4-tetrahydro-isoquinolin-7-yl)-propanoic acid, enantiomer B;

and the corresponding N-oxides and ester prodrugs thereof, and the pharmaceutically acceptable salts and solvates of such compounds, and the N-oxides and ester prodrugs thereof.

36. A pharmaceutical composition comprising an effective amount of a compound according to claim 1 or a corresponding N-oxide or ester prodrug thereof, or a pharmaceutically acceptable salt or solvate of such a compound, or an N-oxide or ester prodrug thereof, in association with a pharmaceutically acceptable carrier or excipient.

37. A method for the treatment of a human or non-human animal patient suffering from, or subject to, a condition which can be ameliorated by the administration of an inhibitor of $\alpha 4\beta 1$ mediated cell

adhesion comprising administering to said patient an effective amount of a compound according to claim 1 or a corresponding N-oxide or ester prodrug thereof, or a pharmaceutically acceptable salt or solvate of such a compound, or an N-oxide or ester prodrug thereof.

- 5 38. A method for the treatment of a patient suffering from, or subject to, asthma comprising administering to said patient an effective amount of a compound according to claim 1 or a corresponding N-oxide or ester prodrug thereof, or a pharmaceutically acceptable salt or solvate of such a compound, or an N-oxide or ester prodrug thereof.
- 10 39. A method for the treatment of a patient suffering from, or subject to, an inflammatory disease comprising administering to said patient an effective amount of a compound according to claim 1 or a corresponding N-oxide or ester prodrug thereof, or a pharmaceutically acceptable salt or solvate of such a compound, or an N-oxide or ester prodrug thereof.
- 15 40. A method for the treatment of a human or non-human animal patient suffering from, or subject to, a condition which can be ameliorated by the administration of an inhibitor of $\alpha 4\beta 1$ mediated cell adhesion comprising administering to said patient an effective amount of a composition according to claim 36.
- 20 41. A method for the treatment of a patient suffering from, or subject to, asthma comprising administering to said patient an effective amount of a composition according to claim 36.
42. A method for the treatment of a patient suffering from, or subject to, an inflammatory disease comprising administering to said patient an effective amount of a composition according to claim 36.